AMENDMENTS

IN THE CLAIMS

Please cancel claims 7, 19-33, and 36-60 without prejudice to subsequent revival.

REMARKS

With this amendment, claims 1, 3-6, 8-18, 34, 35, and 61-63 are pending in the application. Claims 19-33, and 36-60, drawn to a non-elected invention, and claim 7 have been canceled. All pending claims are provided in Appendix A for the Examiner's convenience.

Specification

The disclosure was objected to as making reference to several US patent applications. The status of these applications remains the same. However, as requested by the Examiner, Applicants will update the status of the applications as they change.

Rejection under 35 U.S.C. § 112, second paragraph

"Stringent conditions"

Claim 7 has been rejected as allegedly indefinite for reciting the phrase "stringent conditions." The rejection states that the term is confusing because it "encompasses conditions of varying degrees of stringency." The rejection further claims that stringent conditions are not clearly defined in the specification. To expedite prosecution, claim 7 has been canceled. Applicants therefore respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 101

Claims 1, 3-18, 34, 35, and 61-63 were rejected as allegedly supported neither by a specific and substantial utility, nor by a well-established utility. The rejection states that "the proposed uses of the claimed invention are "simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids." Office Action, page 5, lines 17-19.

Applicants respectfully traverse the rejection. Applicants have disclosed in the present specification that the claimed nucleic acid, a full length cDNA, encodes a G protein coupled receptor ("GPCR") that is specifically expressed in taste buds of the tongue, and have provided data demonstrating that the claimed protein is a functional G-protein coupled receptor. The present invention is therefore useful, e.g., for screening for modulators of a taste bud cell specific GPCR, for the identification of GPCR-B3 ligands, and as a specific marker for specialized taste bud cells of the tongue.

As described in the present specification, full length cDNAs that encode a taste cell-specific nucleic acids were cloned. Sequence analysis of the GPCR-B3 clone showed that it had the structure of a G-protein coupled receptor, with an extracellular domain, seven transmembrane domains, and a cytoplasmic domain (*see, e.g.*, Example I, page 56-57). Subsequently, protein expression patterns were determined for GPCR-B3 using *in situ* analysis (*see, e.g.*, Example II, page 58, and Figure 3). Figure 3 shows that the claimed nucleic acids express proteins that are specifically expressed in taste buds of the tongue.

Furthermore, the specification provides experimental date demonstrating that GPCR-B3 is a functional G-protein coupled receptor. Figure 4 shows the structure of a chimeric protein, comprising an extracellular domain of a murine MGluR1 receptor fused to the seven transmembrane domains and cytoplasmic domains of GPCR-B3. This chimeric GPCR construct was transfected into HEK cells, which were then stimulated with glutamate, the MGluR1 ligand. The HEK cells demonstrated an increase in intracellular calcium in response to the ligand, indicating that the chimeric GPCR couples to a promiscuous G protein and triggers calcium responses that are detectable using the indicator fura-2. The presently claimed "GPCR-B4" nucleic acids therefore encode a G protein coupled receptor that is specifically expressed in circumvallate and foliate cells of the tongue, which are taste bud cells, as described in the specification.

As described ehrein, the claimed nucleic acids encode a taste bud cell specific G-protein coupled receptor. Nucleic acids encoding GPCR-B3 are therefore useful, e.g., in assays for modulators of taste transduction. This use is not merely a "starting point for further research

and investigation," but a direct assay for taste ligands and modulators of taste signal transduction. Furthermore, the claimed nucleic acids are specifically expressed in a unique subset of tongue cells. As such, they have specific and substantial utility as markers for specialized taste cells of the tongue. Such markers are useful for the generation of taste topographic maps the elucidate the relationship between taste bud cells of the tongue and taste sensory neurons leading to taste centers in the brain. Applicants have therefore provided a nucleic acid that encodes a protein with known signaling activity and specific expression in a specialized sub-set of cells. The nucleic acids of the invention therefore have specific, substantial, and credible utility. Applicants therefore respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph: enablement

Claims 1, 3-18, 34, 35, and 61-63 were rejected as allegedly lacking enablement, as the claimed invention is allegedly not supported by either by a specific and substantial asserted utility, or a well established utility. Applicants respectfully traverse the rejection. As described above, the instant claims are well supported by a specific and substantial asserted utility. As the Examiner has provided no other reasoning why the claims lack enablement, Applicants respectfully request that the rejection be withdrawn.

It is well established that the Patent Office bears the initial burden of providing evidence or reasoning why a pending claim does not meet the requirements of §112, first paragraph. A concise statement of the law is provided in *In re Marzocchi* 169 USPQ 367, 369 (C.C.P.A. 1971):

> [A] specification disclosure which contains a teaching of the manner and process of making the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support... It is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable

evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi* 169 USPQ 367,369 (C.C.P.A. 1971).

In the present case, no evidence or reasoning has been provided to explain why one of skill could not practice the claimed invention using the present specification and standard techniques. However, the specification teaches how to make expression vectors encoding the taste-specific G-protein coupled receptors of the invention of the invention, express the vectors, and test for GPCR activity (*see, e.g.*, specification, page 9, lines 11-18; page 12, lines 11-22; page 13, line 30 to page 14, line 16; and page 26-31). The rejection therefore fails to meet the burden of providing clear reasoning why the specification, coupled with that which is well known in the art, would not teach one of skill in the art how to make and use the invention.

Rejection under 35 U.S.C. § 112, first paragraph: written description

Claims 1, 3, 5-18, 34, 35, and 61-63 were rejected as allegedly containing subject matter that was not described in the specification as originally filed. In the Office Action, the Examiner observed that the purpose of the written description requirement is to convey to one of skill in the art that the inventor was in possession of the invention as of the filing date. The rejection then stated that "the skilled artisan cannot envision the detailed chemical structure of the encompassed variants." Office Action, lines 18-19.

Applicants respectfully traverse this rejection. The claims fully comply with the requirements for written description of a chemical genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). The claims set forth both functional elements as well as structural elements, i.e., hybridization conditions and reference sequences to which

members of the claimed genus hybridize. Therefore, the claimed sequences are thereby defined via shared physical and structural properties.

As described above, the present invention relates to the discovery of a nucleic acid encoding a new taste bud specific GPCR, called GPCR-B3. The genus of GPCR-B3 nucleic acids and the proteins that they encode is claimed by reference to shared structural features, i.e., nucleic acid sequences (SEQ ID NO:4, 5, or 6) that encode either the entire GPCR-B3 protein (SEQ ID NO:1, 2 or 3) or conserved structural domains of the GPCR-B protein. The conserved structural features of the GPCR-B3 protein include the extracellular domain, the transmembrane domain, and the intracellular domain. The claims also provide hybridization conditions in which the claimed genus of GPCR-B3 nucleic acids hybridize to the reference conserved sequences, or a specific percent identity to the reference sequence.

The ability of a particular nucleic acid to hybridize under *given conditions* to a reference nucleic acid is a physical/structural property of the nucleic acid, because it relies upon the nucleotide sequence of the molecule (*see, e.g.*, Sambrook, *Molecular Cloning: A Laboratory Manual*, pp. 9.47-9.51 (2nd ed. 1989); *see also* Stryer, *Biochemistry*, pp. 573 (2nd ed. 1975)). As described in Stryer, the transition between hybridization and melting of complementary nucleic acid strands is abrupt and largely sequence dependent. When the temperature of hybridization is provided, one of skill in the art would be able to predict whether or not a given sequence would hybridize to a reference sequence (*see, e.g.*, equations provided in Sambrook, *supra*). Moreover, in the same light, the percent identity of a nucleic acid to a reference sequence is a structural feature, as it relies entirely on the sequence of the molecule.

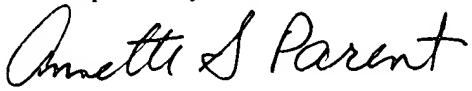
In the present application, Applicants have provided both reference nucleotide sequences, as well as hybridization conditions and sequence analysis algorithms. As required by the standard set forth in *University of California v. Eli Lilly*, these structural features are common to all of the members of the GPCR-B3 polypeptide genus. The conserved sequences encoding structural features of the genus, and the given conditions under which the claimed genus would hybridize to such reference sequences or have a specified identity to such sequences "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed"

(*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 111, 1116 (Fed. Cir. 1991)). The specification thus appropriately describes the claimed GPCR-B3 nucleic acid and protein genus using structural/physical features, as required by the court in *University of California v. Eli Lilly*. As such, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A

PENDING CLAIMS

1. (previously once amended) An isolated nucleic acid encoding a sensory transduction G-protein coupled receptor, the receptor comprising greater than about 70% amino acid identity to an amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the nucleic acid encodes a receptor that specifically binds to polyclonal antibodies generated against SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3.

3. (as filed) The isolated nucleic acid of claim 1, wherein the nucleic acid encodes a receptor that has G-coupled protein receptor activity.

4. (as filed) The isolated nucleic acid of claim 1, wherein the nucleic acid encodes a receptor comprising an amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3.

5. (as filed) The isolated nucleic acid sequence of claim 1, wherein the nucleic acid comprises a nucleotide sequence of SEQ ID NO:4, SEQ ID NO:5, or SEQ ID NO:6.

6. (as filed) The isolated nucleic acid of claim 1, wherein the nucleic acid is from a human, a mouse, or a rat.

8. (as filed) The isolated nucleic acid of claim 1, wherein the nucleic acid encodes a receptor having a molecular weight of about between 92 kDa to about 102 kDa.

9. (previously once amended) An isolated nucleic acid encoding a sensory transduction G-protein coupled receptor, wherein the nucleic acid specifically hybridizes under highly stringent conditions, which end with a wash step at 65°C in a solution comprising 0.2x

SSC and 0.1% SDS, to a nucleic acid having the sequence of SEQ ID NO:4, SEQ ID NO:5, or SEQ ID NO:6.

10. (previously once amended) An isolated nucleic acid encoding a sensory transduction G-protein coupled receptor, the receptor comprising greater than about 70% amino acid identity to a polypeptide having a sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the nucleic acid selectively hybridizes under moderately stringent hybridization conditions, which end with a wash step at 45°C in a solution comprising 1x SSC, to a nucleotide sequence of SEQ ID NO:4, SEQ ID NO:5, or SEQ ID NO:6.

11. (previously once amended) An isolated nucleic acid encoding an extracellular domain of a sensory transduction G-protein coupled receptor, the extracellular domain having greater than about 70% amino acid sequence identity to amino acids 1-563 of SEQ ID NO:1, wherein the extracellular domain specifically binds to polyclonal antibodies generated against amino acids 1-563 of SEQ ID NO:1.

12. (as filed) The isolated nucleic acid of claim 11, wherein the nucleic acid encodes the extracellular domain linked to a nucleic acid encoding a heterologous polypeptide, forming a chimeric polypeptide.

13. (previously once amended) The isolated nucleic acid of claim 11, wherein the nucleic acid encodes amino acids 1-563 of SEQ ID NO:1.

14. (previously once amended) An isolated nucleic acid encoding a transmembrane domain of a sensory transduction G-protein coupled receptor, the transmembrane domain comprising greater than about 70% amino acid sequence identity to amino acids 563 to 812 of SEQ ID NO:1, wherein the transmembrane domain specifically binds to polyclonal antibodies generated against amino acids 563-812 of SEQ ID NO:1.

15. (as filed) The isolated nucleic acid of claim 14, wherein the nucleic acid encodes the transmembrane domain linked to a nucleic acid encoding a heterologous polypeptide, forming a chimeric polypeptide.

16. (previously once amended) The isolated nucleic acid of claim 14, wherein the nucleic acid encodes amino acids 563-812 of SEQ ID NO:1.

17. (previously once amended) The isolated nucleic acid of claim 14, wherein the nucleic acid further encodes a cytoplasmic domain comprising greater than about 70% amino acid identity to amino acids 812 to 840 of SEQ ID NO:1.

18. (previously once amended) The isolated nucleic acid of claim 17, wherein the nucleic acid encodes amino acids 812 to 840 of SEQ ID NO:1.

34. (as filed) An expression vector comprising the nucleic acid of claim 1.

35. (as filed) A host cell transfected with the vector of claim 34.

61. (previously once amended) A method of making a sensory transduction G-protein coupled receptor, the method comprising the step of expressing the receptor from a recombinant expression vector comprising a nucleic acid encoding the receptor, wherein the amino acid sequence of the receptor comprises greater than about 70% amino acid identity to a polypeptide having a sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the receptor specifically binds to polyclonal antibodies generated against SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3.

62. (previously once amended) A method of making a recombinant cell comprising a sensory transduction G-protein coupled receptor, the method comprising the step of transducing the cell with an expression vector comprising a nucleic acid encoding the receptor, wherein the amino acid sequence of the receptor comprises greater than about 70% amino acid identity to a polypeptide having a sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the receptor specifically binds to polyclonal antibodies generated against SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3.

63. (previously once amended) A method of making an recombinant expression vector comprising a nucleic acid encoding a sensory transduction G-protein coupled receptor, the method comprising the step of ligating to an expression vector a nucleic acid encoding the receptor, wherein the amino acid sequence of the receptor comprises greater than about 70% amino acid identity to a polypeptide having a sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the receptor specifically binds to polyclonal antibodies generated against SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3.